DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 16 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
House Committee on Government Reform
House of Representatives
Washington, D. C. 20515-6148

Dear Chairman Souder:

This letter is in final response to follow-up questions to your letter of December 21, 2005. These follow-up questions were forwarded to me electronically by Ms. Michelle Gress on April 3, 2006, after the briefing between representatives from the Food and Drug Administration (FDA or the Agency) and your staff on the drug, Mifeprex, on Friday, March 28, 2006. In a letter dated May 2, 2006, FDA responded to questions 1, 2(d) and (e), 3, 4, and 5. Below and in the enclosed table are the responses to the remaining questions, 2(a), (b), and (c). Your questions are repeated below, followed by the Agency's responses.

2. a) Please list all drugs that have been pulled or withdrawn from the market since 1997 (see attached table for a listing of 1997-2001 drugs).

Marketing can be discontinued by a manufacturer for a number of reasons including business reasons, lack of safety, or lack or efficacy. The table you have provided from the FDA Consumer lists only drugs that are purported to have been withdrawn for safety reasons. Therefore, we interpret your question as requesting a list of drugs that have been pulled or withdrawn from the market from 1997-2005 for what FDA believes or understands to be safety reasons.

b) List and then summarily describe the evidence, studies, and case reports that prompted FDA to conclude that the marketing approval for each drug needed to be withdrawn (e.g., longitudinal studies demonstrating predictable events, epidemiological evidence, adverse event reports, etc.).

For each listed drug, we are providing a summary of the information that we believe led to a decision by either the sponsor or, in some cases, the sponsor and the Agency, that the product should be withdrawn from the market.

c) Please indicate for each withdrawn drug whether and why FDA believed or did not believe that a causal relationship had been demonstrated between the use of the drug in question and the relevant adverse events.

As we indicated in our May 2, 2006, letter to you, the decision to withdraw a drug from marketing, or to withdraw the approval of a drug, is a complex decision that is based on a number of important considerations, of which potential causality is only one. It is often difficult or impossible to determine whether an individual adverse event was "caused by" a drug. However, we are providing a brief description of the safety-related concerns that we believe contributed to the decision, either by the sponsors alone or after discussion with the Agency, to withdraw the products listed.

Thank you for your continued interest in this important issue. If we can be of further assistance, please let us know.

Sincerely,

David W. Boyer
Assistant Commissioner
for Legislation

Enclosure

Drug Name	
2005	
Neutro-Spec (Technetium (99m Tc) fanolesomab)	On December 19, 2005, Palatin Technologies voluntarily suspended sales and marketing of NeutroSpec (Technetium (99m Tc) fanolesomab) in the United States, due to reports of serious and life-threatening cardiopulmonary events following the administration of the drug. NeutroSpec is used for radionuclide imaging of patients with equivocal signs and symptoms of appendicitis. NeutroSpec also has been used for certain unapproved indications, such as the detection of osteomyelitis and other infections. Onset of these serious adverse events generally occurred within minutes of administering the drug and there have been two deaths attributed to cardiopulmonary failure. Patients have experienced other serious cardiopulmonary events, including cardiac arrest, hypoxia, dyspnea, and hypotension, and required resuscitation with fluids, vasopressors, and oxygen. There is no evidence that patients who had already safely received the drug face any long-term risk. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/technetium99/default.htm* As FDA stated in its Public Health Advisory dated 12/19/2005, no definitive determination was made regarding the relationship between NeutroSpec and the reported adverse events. However, the consistent characteristics and rapid onset of the events following NeutroSpec injection made it likely that they were due to administration of NeutroSpec.
Tysabri (nataluzimab)	On February 28, 2005, FDA issued a public health advisory to inform patients and health care providers about the suspended marketing of Tysabri (nataluzimab) while the Agency and the manufacturer evaluated two serious adverse events reported with its use. Tysabri, which received accelerated approval from FDA in November 2004, is indicated for reducing the frequency of exacerbations in patients with relapsing forms of multiple

	sclerosis (MS). FDA received a report from Biogen Idec, the manufacturer of Tysabri, of one confirmed fatal case and one possible case of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri for MS. FDA was given preliminary information about these cases by Biogen, Idec on February 18, 2005. Details became available to FDA the next week. A third case of PML, this one fatal, in a patient treated with Tysabri for Crohn's Disease was identified shortly thereafter. PML is a rare, serious, progressive neurologic disease usually occurring in immunosuppressed patients. There is no known effective treatment for PML. Although the relationship between Tysabri and PML was not known at the time of the public health advisory, because of the serious and often fatal nature of PML, the company, in a decision with which FDA concurred, voluntarily suspended marketing of the drug as well as its use in clinical trials until more detailed information could be gathered. At that time, FDA also placed the ongoing clinical trials on clinical hold. In February 2006, FDA lifted the clinical hold on the ongoing trials, allowing the sponsor to resume administration of natalizumab to patients who had previously been receiving the drug within an IND study at the time of the suspension of use in February 2005. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/natalizumab/default.htm*
Palladone (hydromorphone hydrochloride)	On July 13, 2005, FDA issued a Public Health Advisory to announce that, at FDA's request, Purdue Pharma had agreed to voluntarily suspend sales and marketing of Palladone (hydromorphone hydrochloride) in the United States. Pharmacokinetic data indicate that the co-ingestion of Palladone and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone. These

	elevated levels may be lethal, even in opioid tolerant patients. Palladone is a time-release formulation of hydromorphone, a potent narcotic painkiller. Palladone is taken once-a-day and the capsule slowly releases a steady amount of hydromorphone into the body over that whole day. Palladone is approved for treatment of moderate to severe chronic pain only in opiate-tolerant patients (that is, patients who have been taking opiate containing products for a considerable period of time). Palladone was sold in the U.S. from January 2005 to July 2005, and was used only by a small number of patients. To date, FDA is not aware of any patients who had life-threatening side effects from drinking alcohol while taking Palladone. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/palladone/default.htm*
Cylert (pemoline)	In May 2005, Abbott chose to stop sales and marketing of Cylert (pemoline) (Pemoline tablets and chewable tablets)in the U.S. All companies manufacturing generic versions of Cylert also agreed to stop sales and marketing of this product. Cylert is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This product was considered second line therapy for ADHD because of its association with life threatening hepatic failure. As of October 2005, FDA was aware of 13 reports of liver failure resulting in liver transplant or death, usually within four weeks of onset of signs and symptoms of liver failure. Although the absolute number of reported cases of liver failure with pemoline is not large, the reporting rate for liver failure with pemoline is 10 to 25 times greater than the background rate of liver failure in the general population. Despite diminished use of Cylert and generic pemoline products since the addition of the boxed warning in 1999 and restrictive labeling (e.g., boxed warning, second line therapy,

	Medication Guide), a risk of liver failure remained (FDA was aware of 1 new case of pemoline-associated liver failure since the introduction of the boxed warning in 1999). Given the availability of multiple other drug treatments for ADHD, including 1 that is not scheduled and several products that can be given once a day, FDA concluded that the risk of liver failure with this drug outweighed the potential benefits. See the following website for additional information: *http://www.fda.gov/cder/drug/InfoSheets/HCP/pemolineHCP.htm*
Bextra (valdecoxib)	On April 7, 2005, FDA announced that it had requested that Pfizer voluntarily withdraw Bextra (valdecoxib) from the U.S. market. Pfizer agreed to suspend sales and marketing of Bextra in the U.S., pending further discussion with the Agency. At that time, the Agency had concluded that the overall risk versus benefit profile of Bextra was unfavorable. This conclusion was based on the potential increased risk for serious cardiovascular (CV) adverse events, which appears to be a class effect of non-steroidal anti-inflammatory drugs (NSAIDs) (excluding aspirin), an increased risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other NSAIDs, and the fact that Bextra had not been shown to offer any unique advantages over the other available NSAIDs. Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in two short-term trials in patients immediately post-operative from coronary artery bypass graft (CABG) surgery. Data were not available from long-term controlled clinical trials to evaluate the cardiovascular safety of Bextra following chronic use. FDA concluded that it was reasonable to extrapolate the adverse CV risk information for Bextra from the short-term CABG trials to chronic use given the fact that other COX-2 selective NSAIDs have been shown in long-term controlled clinical trials to be associated with an increased risk of serious adverse CV events (e.g., death, MI, stroke), and the well described

	risk of serious, and often life-threatening gastrointestinal bleeding. Bextra is a sulfonamide and already carried a boxed warning in the package insert for serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). The reporting rate to FDA's spontaneous reporting system for these serious skin reactions was significantly greater for Bextra than other COX-2 selective agents. The risk of these serious skin reactions in individual patients was unpredictable, occurring in patients with and without a history of sulfa allergy, and after both short- and long term use. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/COX2*
2004	
Vioxx (rofecoxib)	On September 30, 2004, Merck & Co., Inc. announced a voluntary withdrawal of Vioxx (rofecoxib) from the U.S. market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx. FDA also issued a Public Health Advisory on that same day. Vioxx, a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID), was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms. It was also approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children. The Data Safety Monitoring Board for an ongoing long-term study of Vioxx (APPROVe) had recommended that the study be stopped early for safety reasons. The study, which was being conducted in patients at risk for developing recurrent colon polyps, showed an increased risk of cardiovascular events (including heart attack and stroke) in patients on

Vioxx compared to placebo, particularly those who had been taking the drug for longer than 18 months.

In June 2000, Merck submitted to FDA a safety study called VIGOR (Vioxx Gastrointestinal Outcomes Research) that found an increased risk of serious cardiovascular events, including heart attacks and strokes, in patients taking Vioxx compared to patients taking naproxen. After reviewing the results of the VIGOR study and other available data from controlled clinical trials, FDA consulted with its Arthritis Advisory Committee in February 2001 regarding the clinical interpretation of this new safety information. In April 2002, labeling for Vioxx was changed to reflect the findings from the VIGOR study. The labeling changes included information about the increase in risk of cardiovascular events, including heart attack and stroke.

Other studies in patients taking Vioxx also suggested an increased risk of cardiovascular events. FDA was in the process of reviewing the results to determine whether further labeling changes were warranted when Merck informed the agency of the results of the new trial and its decision to withdraw Vioxx from the market.

In April 2005, following a thorough review of the available data, FDA stated in its decision memorandum that there was evidence that Vioxx, along with the other approved COX-2 selective NSAIDs, was associated with an increased risk of serious cardiovascular events (e.g., MI, stroke, and death) when compared with a placebo.

See the following website for additional information:
http://www.fda.gov/cder/drug/infopage/COX2/default.htm

2003

Trovan (trovafloxacin/alatrofloxacin)	In June 1999, FDA issued a Public Health Advisory to inform physicians and the public that, based on safety data related to liver injury, Trovan, (trovafloxacin/alatrofloxacin) an antibiotic used to treat many different types of infections, should only be used to treat patients who had certain serious and life or limb-threatening infections as outlined in the PHA. In the clinical studies of Trovan approximately 7,000 patients were exposed to the drug. No cases of acute liver failure were reported in these pre-market clinical trials. Following the marketing of Trovan in the United States in February 1998, FDA began receiving reports of patients who experienced serious liver reactions in association with use of the product. In July 1998, FDA worked with the manufacturer to add further information about this toxicity of the drug to Trovan's label, or package insert, in order to inform practitioners. Subsequently, FDA received over 100 reports of cases of patients who were ill with symptoms of liver toxicity, in addition to others in which patients were without symptoms. Some of these patients developed serious liver injury leading to liver transplant and/or death. FDA was aware of 14 cases in patients whose livers actually failed to function that were strongly associated with Trovan exposure. Trovan-associated liver failure appeared to be unpredictable with regard to treatment duration, patient age or sex, and type of infection. Also, when use exceeded two weeks there appeared to be a substantial increase in risk of this toxicity. Liver failure also had been reported following Trovan re-exposure after some period of being off the drug.

	In December 2003, the company voluntarily requested withdrawal of their NDAs. See the following websites for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/ANS00958.html* *http://www.fda.gov/cder/news/trovan/default.htm*
Orlaam (levomethadyl acetate HC)	Roxane issued a Product Discontinuation Notice on August 23, 2003, stating that it was discontinuing the sale and distribution of the product after current inventory was depleted. Orlaam (levomethadyl acetate HC) was, a synthetic opioid agonist solution indicated for the management of opiate dependence, reserved as second-line therapy for the treatment of opiate-addicted patients who fail to show acceptable response to other adequate treatments for opiate addiction. It was removed from the European market in March 2001 following reports of severe cardiac-related adverse events, including QT interval prolongation, Torsades de Pointes and cardiac arrest. Other available first-line treatment options for the management of opiate dependence include methadone and buprenorphine. See the following website for additional information: *http://www.fda.gov/cder/drug/shortages/orlaam.htm*

2002

Tegison (etretinate)	In March 1998, Hoffman-La Roche voluntarily discontinued marketing Tegison (etretinate), a treatment for severe recalcitrant psoriasis, after an alternative, Soriatane, became available. The company requested withdrawal of its NDAs in 1999 and FDA published the notice of withdrawal in the Federal Register in 2003. In that notice, FDA stated that etretinate had been removed from the market for safety reasons because the product posed a greater risk of birth defects than acitretin, the active metabolite of etretinate used in its replacement product.

2001

Baycol (cerivastatin)	On August 8, 2001, FDA announced that Bayer Pharmaceutical Division was voluntarily withdrawing Baycol (cerivastatin) from the U.S. market because of reports of sometimes fatal rhabdomyolysis, a severe muscle adverse reaction from this cholesterol-lowering (lipid-lowering) product. FDA agreed with and supported this decision. Baycol, which was initially approved in the U.S. in 1997, is a member of a class of cholesterol lowering drugs that are commonly referred to as "statins." Statins lower cholesterol levels by blocking a specific enzyme in the body that is involved in the synthesis of cholesterol. While all statins have been associated with very rare reports of rhabdomyolysis, cases of fatal rhabdomyolysis in association with the use of Baycol have been reported significantly more frequently than for other approved statins. Fatal rhabdomyolysis reports with Baycol had been reported most frequently when used at higher doses, when used in elderly patients, and particularly, when used in combination

	with gemfibrozil (LOPID and generics), another lipid lowering drug. FDA received reports of 31 U.S. deaths due to severe rhabdomyolysis associated with use of Baycol, 12 of which involved concomitant gemfibrozil use. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/baycol/default.htm*
Raplon (rapacuronium bromide)	On March 27, 2001, Organon Inc announced its intention to voluntarily withdraw the injectable anesthesia drug RAPLON (rapacuronium bromide) withdrawn from the market in light of the product's possible association with the occurrence of bronchospasm - a mild to severe inability to breathe normally that can lead to permanent injury or death. Five deaths, reported to the manufacturer, occurred during the administration of Raplon. FDA approved RAPLON for this indication in August 1999 after more than a year-long review of Organon's new drug application. Although the drug's approved labeling did note the occurrence of bronchospasm in a small percentage of clinical trial patients receiving the drug, post-marketing reports indicated that the risk of injury from bronchospasm might be greater than was suggested in clinical trials. See the following websites for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01072.html* *http://www.fda.gov/medwatch/SAFETY/2001/raplon_DDL.htm*

2000	
Lotronex (alosetron)	On November 28, 2000, Glaxo Wellcome informed FDA that it was voluntarily withdrawing Lotronex (alosetron hydrochloride) tablets from the market. The company's action followed a meeting held earlier that day with FDA where the agency discussed with Glaxo Wellcome risk management options that included restricting the distribution of the drug or marketing withdrawal. Specifically, FDA had been concerned about reported cases of intestinal damage resulting from reduced blood flow to the intestine (ischemic colitis) and severely obstructed or ruptured bowels (complications of severe constipation). As of November 10, 2000, FDA had received and reviewed a total of 70 cases of serious post-marketing adverse events, including 49 cases of ischemic colitis and 21 cases of severe constipation. Of the 70 cases, 34 resulted in hospitalization without surgery, 10 resulted in surgical procedures, and three resulted in death. FDA had received two additional reports of death that the Agency did not classify as being cases of ischemic colitis or severe complications of constipation. Prior to approval, four cases of ischemic colitis were observed in clinical studies and were discussed at a November 1999 meeting of FDA's Gastrointestinal Drugs Advisory Committee. These cases were transient, mild-to-moderate in nature and reversible upon discontinuation of the drug. On June 27, 2000, FDA convened a public advisory committee meeting where risk management options in response to the serious adverse events reported up to that point were discussed. No deaths were reported up to that date. The consensus of the advisory committee members was that both physicians and patients must be informed of the potentially serious adverse events associated with Lotronex. In August 2000, FDA announced that the labeling for the product was being updated, and would include a Medication Guide (patient labeling) that warned patients directly about the

	risks associated with the drug. In addition, Glaxo Wellcome issued "Dear Healthcare Professional" and "Dear Pharmacist" letters to advise these groups of the important new information. FDA continued to receive severe adverse event reports of ischemic colitis and complications of constipation associated with Lotronex. In addition, FDA received reports of death and more serious complications of ischemic colitis that required blood transfusion or surgery. The company voluntarily withdrew the drug from the market in November 2000, but later submitted a supplemental New Drug Application (sNDA) that allowed restricted marketing of Lotronex (alosetron hydrochloride), to treat only women with severe diarrhea-predominant irritable bowel syndrome (IBS) which was approved on June 7, 2002. The approved sNDA for Lotronex includes a risk management program to ensure patients and physicians are fully informed of risks and possible benefits of Lotronex. See the following website for more information: *http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm*
Propulsid (cisapride)	On April 12, 2000, Janssen Pharmaceutica announced that, because of the risk of serious cardiac arrhythmias and death associated with the use of Propulsid in certain patients, Janssen, in consultation with FDA, had decided to discontinue marketing Propulsid as of July 14, 2000, and make it available only through an investigational limited access program. Propulsid was approved for treatment of night-time heartburn due to gastroesophageal reflux disease. Propulsid had been associated with serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. From July 1993 through December 1999, 341 such cases were spontaneously reported,

	including 80 deaths. In approximately 85 percent of these cases the events occurred when Propulsid was used in patients with known risk factors. In the few years preceding its announcement, Janssen had implemented labeling changes and sponsored educational programs to help assure the safe and appropriate use of Propulsid. However, the level of adverse event reporting and risks associated with the drug did not sufficiently decrease. Consequently, Janssen decided to stop marketing the drug and make it available only through an investigational limited access program. See the following websites for additional information: *http://www.fda.gov/medwatch/safety/2000/propul1.htm* *http://www.fda.gov/bbs/topics/ANSWERS/ANS01007.html*
Phenylpropanolamine	Phenylpropanolamine (PPA) is a drug that was used in many over-the-counter (OTC) and prescription cough and cold medications as a decongestant and in OTC weight loss products. In May 2000, scientists at Yale University School of Medicine issued a report entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project." This study reported that taking PPA increases the risk of hemorrhagic stroke (bleeding into the brain or into tissue surrounding the brain) in women. Men also may be at risk. In October 2000, FDA's Nonprescription Drugs Advisory Committee discussed the Yale study along with additional information on PPA. The Advisory Committee, after reviewing the available information, recommended that PPA be considered not safe for OTC use. In November 2000, FDA issued a Public Health Advisory on products containing PPA. Although the risk of hermorrhagic stroke is very low, FDA recommended that consumers not use any products that contain PPA and requested that all drug companies discontinue

	marketing products containing PPA. In response to this request, many companies voluntarily reformulated and are continuing to reformulate their products to exclude PPA while FDA proceeds with the regulatory process necessary to remove PPA from the market. On August 14, 2001, FDA published a proposal in the Federal Register to withdraw approval of all PPA new drug applications and abbreviated new drug applications. On December 22, 2005, FDA issued a notice of proposed rulemaking (notice) for over-the-counter (OTC) nasal decongestant and weight control products containing PPA preparations. This proposed rule would reclassify PPA as nonmonograph (Category II) not generally recognized as safe and effective. See the following website for additional information: *http://www.fda.gov/cder/drug/infopage/ppa/default.htm*
Rezulin (troglitazone)	On March 21, 2000, FDA announced that it had asked and the manufacturer had agreed to withdraw Rezulin (troglitazone) -- a drug used to treat type 2 diabetes mellitus-- from the market. FDA took this action after its review of safety data on Rezulin and two similar drugs, rosiglitazone (Avandia) and pioglitazone (Actos), showed that Rezulin was more toxic to the liver than the other two drugs. Data showed that Avandia and Actos, both approved in the year before the withdrawal of Rezulin, offered the same benefits as Rezulin without the same risk. Severe liver toxicity had been known to occur with Rezulin since 1997. In consultation with

	FDA, Parke-Davis had strengthened the drug's labeling several times and had recommended close monitoring of liver function in patients taking Rezulin. In March 1999, FDA's Endocrine and Metabolic Drugs Advisory Committee reviewed the status of Rezulin and its risk of liver toxicity and recommended continued availability of this drug in a select group of patients -- patients not well-controlled on other diabetes drugs. FDA continued to actively monitor adverse events associated with Rezulin, as well as Avandia and Actos. After nine months of marketing experience with these two newer drugs, FDA stated that it had become clear that these newer drugs had less risk of severe liver toxicity than Rezulin. See the following website for additional information: *http://www.fda.gov/bbs/topics/NEWS/NEW00721.html*
1999	
Hismanal (astemizole)	In June 1999, Janssen Pharmaceutica, Inc. announced that it was voluntarily withdrawing the prescription antihistamine, Hismanal (astemizole) 10 mg., from the market. Since the drug's approval in 1988, new adverse reaction data had required a series of labeling changes and warnings. In light of the choices of other prescription antihistamines available, and the overall risk benefit profile of this drug, FDA supported the decision of the company to withdraw the product. The Agency published a Federal Register notice on August 23, 1999 (64 FR 45973) announcing its determination that the product was withdrawn from sale for safety reasons. In that notice, FDA stated that its review of the withdrawal had considered the sponsor's explanation of the basis for the withdrawal and information available to the Agency regarding the product. See the following website for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/ANS00961.html*

Raxar (grepafloxacin)	On October 27, 1999, Glaxo Wellcome announced that, effective immediately, it was voluntarily withdrawing its oral fluoroquinolone antibiotic, Raxar (grepafloxacin), as a result of emerging safety concerns. In coming to this decision the company stated that it recognized the need to strike a balance between the therapeutic benefits of the medicine, the potential risk of side effects, and the availability of alternative treatments. Raxar was indicated for the treatment of a variety of infections including pneumonia, bronchitis, and some sexually transmitted infections. In its press release announcing the withdrawal, Glaxo Wellcome stated that, in line with the company's practice, it had monitored the safety profile of Raxar since launch, and observed a small number of severe cardiovascular events among patients. While the reported incidence of such cardiovascular events was infrequent, the company stated it was no longer convinced that the benefits of Raxar outweighed the potential risk to patients, given the availability of alternative antibiotics. See the following website for additional information: *http://www.fda.gov/medwatch/safety/1999/raxar.html*
1998	
Posicor (mibefradil)	In June 1998, Roche Laboratories announced that it was voluntarily withdrawing its heart drug Posicor(mibefradil), from the market as a result of new information about potentially harmful interactions with other drugs. Posicor, which was approved for use in the treatment of patients with hypertension and chronic stable angina, reduced the activity of certain liver enzymes that are important in helping the body eliminate many other drugs.

	However, inhibiting these enzymes can cause some of these drugs to accumulate to dangerous levels in the body. See the following websites for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/ANS00876.html* *http://www.fda.gov/medwatch/safety/1998/poscor.htm* The company stated in its press release that its action followed its analysis of the preliminary results of a three-year long-term study of Posicor in congestive heart failure. The study, which was designed to assess Posicor's efficacy for a different indication than those approved, provided further information on drug interactions. The company stated that, although in principle drug interactions can be addressed by appropriate labeling, with respect to Posicor, it believed that the complexity of such prescribing information would make it difficult to implement.
Duract (bromfenac)	On June 22, 1998, Wyeth-Ayerst Laboratories announced that it was voluntarily withdrawing the analgesic, Duract (bromfenac) from the market. The action followed postmarketing reports of rare severe liver failure in patients in whom the drug was used for extended periods of time which was not in accordance with labeling instructions. The new drug application for Duract, a non-steroidal anti-inflammatory drug (NSAID), was submitted to FDA in l994 and was approved in July l997 for short term management of acute pain (use for 10 days or less). It was never approved as a treatment for longer term use for chronic conditions such as osteoarthritis or rheumatoid arthritis. No cases of serious liver injury were reported in clinical trials, however, because there was a higher incidence of liver enzyme elevations in patients treated long term in clinical trials, the product was approved for use for 10 days or less. The information about the elevated

	liver enzymes was included in the product's labeling. After Duract was marketed, FDA and the company received reports of several cases of rare severe hepatitis and liver failure (some requiring transplantation) in patients taking the drug for more than 10 days. In February l998, in response to the reports of severe liver failure (and transplants), FDA and the company strengthened the warnings in Duract's labeling with a special black box warning and Wyeth-Ayerst issued a Dear Doctor letter. The revised label re-emphasized that patients should not take the drug for more than 10 days and alerted physicians and other health care professionals to the cases of severe hepatitis and liver failure (and cases in which patients required a transplant) in patients who had taken Duract. Despite these efforts, the agency and the company continued to receive reports of severe injuries and death with long term use of Duract. Given the availability of other therapies, FDA and Wyeth-Ayerst concluded that it would not be practical to implement the restrictions necessary to assure the safe use (less than 10 days) of Duract. The company and FDA agreed that it would be prudent to withdraw the drug from the market. Wyeth-Ayerst advised doctors to discontinue prescribing and dispensing Duract immediately. See the following websites for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html* *http://www.fda.gov/cder/news/duract/qa.htm*
Seldane	On December 29, 1997, following FDA's announcement of the approval of the prescription antihistimine/decongestant Allegra-D (fexofenadine/ pseudoephedrine)

(terfenadine) and Seldane-D **See attached references.	extended release tablet and also given the previous approval of Allegra, the manufacturer announced its plans to remove the drugs' predecessors, Seldane and Seldane-D (terfenadine-containing products), from the marketplace. Fexofenadine, an active ingredient in Allegra and Allegra-D, is the primary active derivative of terfenadine produced in the body when Seldane and Seldane-D are taken. Fexofenadine provides nearly all of terfenadine's beneficial effects but does not appear to cause a potentially fatal heart condition when taken with some other commonly prescribed medications. In January 1997, FDA proposed removing all terfenadine products from the marketplace because of the approval of a safer alternative drug: fexofenadine. At that time, FDA advised patients currently taking Seldane, Seldane-D and generic terfenadine products to talk to their doctors about switching to alternative medications. In September 1997, the manufacturer added increased warnings on Seldane and Seldane-D's label to give health care providers and consumers who still used terfenadine-containing products the latest available information about these risks, while FDA continued the administrative process of removing these products from the market. The Agency published a notice of withdrawal for safety reasons in the Federal Register on October 5, 1998. See the following website for additional information: *http://www.fda.gov/bbs/topics/ANSWERS/ANS00843.html* FDA's FR notice announcing the intent to withdraw approval of products containing terfenadine explained that the agency believed there was a causal relationship between the concomitant use of terfenadine with drugs that inhibit a particular metabolic pathway (CYP3A4), with the resulting elevated circulating terfenadine levels and change in cardiac potassium channels causing QT prolongation and Torsades de pointes (a particularly dangerous cardiac arrhythmia). .

1997

Pondimin (fenfluramine)

and

Redux

(dexfenfluramine)

On September 15, 1997, FDA, acting on evidence about significant side-effects associated with fenfluramine and dexfenfluramine, announced that it had asked the manufacturers to voluntarily withdraw both treatments for obesity from the market. Dexfenfluramine was manufactured for Interneuron Pharmaceuticals and marketed under the name of Redux by Wyeth-Ayerst Laboratories, a subsidiary of American Home Products Corp. of Madison, N.J., which also manufactured and marketed fenfluramine under the brand name Pondimin. Both companies agreed to voluntarily withdraw their drugs.

FDA stated that the action was based on findings from doctors who had evaluated patients taking these two drugs with echocardiograms, a special procedure that can test the functioning of heart valves. These findings indicated that approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. This was a much higher than expected percentage of abnormal test results.

These findings suggested fenfluramine and dexfenfluramine were the likely cause of heart valve problems of the type that prompted two earlier warnings by FDA concerning "fen-phen," a combination of fenfluramine and phentermine. "Fen-phen" had been widely used off-label for the long-term management of obesity.

In July 1997, researchers at the Mayo Clinic and Mayo Foundation reported 24 cases of rare valvular disease in women who took the "fen-phen" combination therapy. FDA alerted medical doctors that it had received nine additional reports of the same type, and requested all health care professionals to report any such cases to the Agency's MedWatch program or to the respective pharmaceutical manufacturers.

Subsequently, FDA received 66 additional reports of heart valve disease associated mainly with "fen-phen." There were also reports of cases seen in patients taking only fenfluramine

or dexfenfluramine.

See the following websites for additional information:
http://www.fda.gov/cder/news/phen/fenphenpr81597.htm
http://www.fda.gov/cder/news/phen/fenphenqa2.htm